REMARKS

In the Office Action dated September 30, 2004, the Examiner rejected claim 26 under 35 U.S.C. 102(e) "as being anticipated by Hausheer, USP 5910491." Specifically, the Examiner asserted that: "Although the proviso does remove the conflict, the first species of claim 26 still falls within the ambit of the claims of 5910491." Applicants have amended claim 26 to obviate the Examiner's rejection.

The Examiner also rejected claims 14-38 under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner asserted that:

> 1. The term 'on or' at next to last line of claim 14 is in error. Presumably 'one of' was intended.
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> 2. The sole independent claim, claim 14, is a method clam, yet new claim 28 says, 'the compound of...' It is unclear what is intended.
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> 3. The terminology of 'cancer patient or a leukemia patient' is unclear. Leukemia is a form of cancer, cancer of the blood forming tissues. Or is some more specialized definition of cancer intended?
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> 4. Most of the species in claim 26 violate the new claim 14 proviso. For example, many, e.g. $4^{th} - 6^{th}$ species have three variables as H, one as Hal, and thus have no substituent which meets the requirement of the claim 14 proviso.

Applicants have amended the claims to obviate the Examiner's rejections.

The Examiner also rejected claims 14-25, 27-38 under 35 U.S.C. 112, first paragraph, "as failing to comply with the written description requirement". Specifically, the Examiner asserted that:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> A. The choices of Rl or R2 as alkylaminoalkyl, haloalkyl, hydroxyalkyl, alkylamino, and dialkylamino appear to be new matter. Where are such groups specifically described in the specification?
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> B. The proviso is clearly new. The proviso lacks description. Even a negative limitation requires description, Ex Parte Grasselli, 231 USPQ 393. The concept of the definition of these variables depending on each other is entirely new. The fact that most species violate this proviso is further evidence of the lack of description of this material.

Applicants respectfully traverse the Examiner's rejection.

Support for R^1 or R^2 as alkylaminoalkyl, haloalkyl, hydroxyalkyl, alkylamino, and dialkylamino can, for example, be found on page 7 of the specification (and elsewhere) as follows:

> The groups set forth above, can be substituted with a wide variety of substituents to synthesize camptothecin analogs retaining activity. For example, alkyl groups may preferably be substituted with a group or groups including, but not limited to, a benzyl group, a phenyl group, an alkoxyl group, a hydroxyl group, an amino group (including, for example, free amino groups, alkylamino, dialkylamino groups and arylamino groups), an alkenyl group, an alkynyl group and an acyloxy group. In the case of amino groups (-NR^aR^b), R^a and R^b are preferably independently hydrogen, an acyl group, an alkyl group, or an aryl group. Acyl groups may preferably be substituted with (that is R^f is) an alkyl group, a haloalkyl group (for example, a perfluoroalkyl group), an alkoxyl group, an amino group and a hydroxyl group. Alkynyl groups and alkenyl groups may preferably be substituted with (that is, R^g and R^h are preferably) a group or groups including, but not limited to, an alkyl group, an alkoxyalkyl group, an amino alkyl group and a benzyl group.

Moreover, Applicants respectfully assert that the proviso "wherein at least one of R^1, R^2, R^3 and R^4 is not H, a halogen, an alkyl group, an amino group or a nitro group" does not violate the adequate description requirement of 35 U.S.C. 112. In that regard, the adequate description requirement of the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention. As set forth in Ex parte Robert E. Parks and Robert L. Marietta, 30 U.S.P.Q.2D (BNA) 1234, 1236 (Bd. Pat. App. & Inter. 1993):

> The initial burden of establishing a prima facie basis to deny patentability to a claimed invention on any ground is always upon the examiner. In re Oetiker, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In rejecting a

> claim under the first paragraph of 35 U.S.C. 112 for lack of adequate descriptive support, it is incumbent upon the examiner to establish that the originally-filed disclosure would not have reasonably conveyed to one having ordinary skill in the art that an appellant had possession of the now claimed subject matter. Wang Laboratories, Inc. v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993). Adequate description under the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention. In re Herschler, 591 F.2d 693, 200 USPQ 711 (CCPA 1979); In re Edwards, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978); In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed. In re Anderson, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

In Ex parte Robert E. Parks and Robert L. Marietta, the examiner contended that the rejected claims lacked adequate descriptive support because there was no literal basis for the claim limitation "in the absence of a catalyst." The Board of Patent Appeals and Interferences held that "clearly, the observation of a lack of literal support does not, in and of itself, establish a prima facie case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112." In distinguishing Ex Parte Grasselli, 231 USPQ 393 (Bd.App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984), the Board of Patent Appeals and Interferences indicated:

> We are not unmindful of the decision in Ex parte Grasselli, 231 USPQ 393 (Bd.App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984), which involved claims to a process for the ammoxidation of propane or isobutane employing a catalyst 'free of uranium and the combination of vanadium and phosphorus.' Under the particular facts in that case, it was held that the negative limitation introduced new concepts in violation of the description requirement of the first paragraph of 35 U.S.C. 112, citing In re Anderson, supra. In the situation before us, it cannot be said that the originally-filed disclosure would not have conveyed to one having ordinary skill in the art that appellants had possession of the concept of conducting the decomposition step generating nitric acid in the absence of a catalyst.

Clearly, the addition of the proviso in claim14 of the present invention introduces no new concept(s) or new compound for use in the method of the present invention in violation of the description requirement of the first paragraph of 35 U.S.C. 112. In the proviso, Applicants have merely excluded certain compounds from the coverage of the

method of Claim 14. Prior to the addition of the proviso, the description requirement of the first paragraph of 35 U.S.C. 112 was clearly satisfied for each of the compounds covered by Claim 14. The description requirement is not and cannot be violated by excluding certain adequately described compounds from such coverage. In that regard, Applicants request that the Examiner indicate for which compound included in the method of Claim 14 (as amended by addition of the proviso) the description requirement of the first paragraph of 35 U.S.C. 112 is violated. The originally-filed disclosure clearly conveyed to one having ordinary skill in the art that Applicants had possession of the concept of the method of claim 14 for each of the compounds covered by claim 14 as amended. The first paragraph of 35 U.S.C. 112 requires no more.

Applicants further respectfully assert that the Applicants could set forth the exact same claim coverage now set forth in claim 14 without the proviso of claim 14 asserted by the Examiner to lack description by setting forth multiple independent claims in which the groups restricted by the proviso are simply removed from the claim coverage. This assertion is best illustrated through use of a simplified example. In that regard, assume for the purposes of the example that an amended Claim A sets forth:

> Claim A. A compound having the formula $R^aZZ'R^b$, wherein R^a and R^b are independently, H, alkyl, aryl, or amino, wherein at least one of R^a and R^b is not H.

In the above example, Claim A is shown with the amendment to its original text marked (that is, the underlined addition of the proviso). The above claim coverage can equivalently be set forth in the following two claims (Claim A1 and A2), which do not include the negative proviso:

> Claim A1. A compound having the formula $R^aZZ'R^b$, wherein R^a is H, alkyl, aryl, or amino and R^b is alkyl, aryl, or amino.
>
> Claim A2. A compound having the formula $R^aZZ'R^b$, wherein R^a is alkyl, aryl, or amino and R^b is H, alkyl, aryl, or amino.

Assuming there is no literal description of the proviso "wherein at least one of R^a and R^b is not H", could the Examiner assert that Claim A violated the description requirement of the first paragraph of 35 U.S.C 112, when the coverage of Claim A is identical to the

combined coverage of Claims A1 and A2, which clearly would not violate the description requirement of the first paragraph of 35 U.S.C 112?

It is the scope of the claimed subject matter that must be described in the specification and not the literal language used to set forth that claimed subject matter. Applicants respectfully assert that claim 14, as amended, does not violate the description requirement of the first paragraph of 35 U.S.C. 112 as the method of treatment for each compound covered thereby was clearly described in the specification as originally filed.

The Examiner also rejected claims 28-40 under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 1-14 of U.S. Patent No. 6150343." Specifically, the Examiner asserted that: "Although the conflicting claims are not identical, they are not patentably distinct from each other because these claims are just slightly broader versions of the patent claims of the parent. The rejected claims all have the 10-OH feature required in the patent." Applicants respectfully traverse the Examiner's rejection.

U.S. Patent No. 6150343 claims 7-silyl comptothecin compounds including a 10-OH substituent. Applicants respectfully assert that claims setting forth such compounds do not render obvious the use of such compounds and other compounds in treatment of malignant melanoma, stomach cancer, breast cancer, ovarian cancer, lung cancer, colorectal cancer or leukemia. In that regard, claims 28-40 has been amended to be method claims.

The Examiner rejected claims 28-40 under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 1-8 of U.S. Patent No. 6455699.". Specifically, the Examiner asserted that:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because these claims are just slightly broader versions of the patent claims of the parent. The rejected claims all fall into either claim 1, claim 2, claim 3 or claim 4." Applicants respectfully traverse the Examiner's rejection.

> Assuming that claims 28-40 are intended as compound claims, this rejection would still be valid. This can be overcome by making all these claims as method claims."

U.S. Patent No. 6455699 also claims 7-silyl comptothecin compounds including various A-ring substituents. Applicants respectfully assert that claims setting forth such compounds do not render obvious the use of such compounds and other compounds in treatment of malignant melanoma, stomach cancer, breast cancer, ovarian cancer, lung cancer, colorectal cancer or leukemia. In that regard, claims 28-40 has been amended to be method claims.

The Examiner further rejected Claims 14-40 under 35 U.S.C. 112, first paragraph, "as failing to comply with the enablement requirement." Specifically, the Examiner asserted that:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
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> Claims 28-40 are included on the assumption that these are really intended as method claims."
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> Pursuant to In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is 'undue'; see In re Vaeck, 20 USPQ2d 1438, 1444. The analysis is as follows:
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> (1) Breadth of claims.
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> (a) Scope of the compounds. This varies according to claim. Claim 14, because of the substantial scope of the 8 primary variables, covers billions of compounds. Claims 26, 29 and 30 cover only a few species.

(b) Scope of the diseases covered. The coverage is immense. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that 'the scope of enablement varies inversely with the degree of unpredictability of the factors involved,' and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is deficient. The dosage range information was omitted from the specification. The issue is discussed in general terms in the paragraph bridging pages 22-23, but no actual numbers appear there.

(4) State of the Prior Art: The claimed compounds are camptothecins. No camptothecin has ever been found to be effective against cancer generally or leukemia generally.

(5) Working Examples: No actual working examples for the treatment of cancer are presented. Data appears for 3 cell lines, one of which is a leukemia line. However, the most potent species (2, 7-10, 15) are all excluded by proviso. However, one cell line cannot possible demonstrate leukemia generally, given the huge diversity of leukemias.

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of spurces, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not generally treatable. As an example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. That is, there is no one compound that can treat these generally, or even most of them, nor is there any reason to think that there could be such a compound. Since it is beyond the skill of oncologists today to get an agent

to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. As an example, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. The majority of common cancers do not respond to chemotherapy. With regard to leukemia: Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These include viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia. There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-BCR- myeloid leukemia, acute basophilic leukemia, acute myleofibrosis, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and many others. No compound has ever been found effective generally against leukemias because they are simply too diverse.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1 and 6, the quantity of experimentation needed is expected to be great.

> MPEP 2164.01 (a) states, 'A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.' In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Applicants respectfully traverse the Examiner's rejection

The Examiner objected to claims 39-40 "as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims."

Initially, Applicants have amended the claims to set forth a method of treating a patient having malignant melanoma, stomach cancer, breast cancer, ovarian cancer, lung cancer, colorectal cancer or leukemia. Camptothecin analogs have been shown to have activity against such conditions. With respect to dosage information, in addition to the general knowledge of dosage (including, dosage for other camptothecin analogs) know to those skilled in the art, it is, for example, set forth on page 10 of the specification that:

> The present invention also provides a method of treating a patient, which comprises administering a pharmaceutically effective amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof. The compound may, for example, be administered to a patient afflicted with cancer and/or leukemia by any conventional route of administration, including, but not limited to, intravenously, intramuscularly, orally, subcutaneously, intratumorally, intradermally, and parenterally. The pharmaceutically effective amount or dosage is preferably between 0.01 to 60 mg of the compound of formula (1) per kg of body weight. More preferably, the pharmaceutically effective amount or dosage is preferably between 0.1 to 40 mg of the compound of formula (1) per kg of body weight. In general, a pharmaceutically effective amount or dosage contains an amount of a compound of formula (1) effective to diaplay antileukemic and/or antitumor (anticancer) behavior. Pharmaceutical compositions containing as an active ingredient a compound of formula (1) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier or diluent are also within the scope of the present invention.
>
> The present invention also provides a pharmaceutical composition comprising any of the compounds of formula (1) and a pharmaceutically

acceptable carrier. The composition may contain between .1 mg and 500 mg of the compound of formula (1), and may be constituted into any form suitable for the mode of administration.

With respect to the scope of the claims, Applicants respectfully assert that one skilled in the art would know that each of the compounds set forth in the claimed method is biologically active in the claimed method given the examples provided in the specification and the known structure/activity relationships of camptothecin compounds. With respect to the quantity of experimentation required, the examiner is correct that historically the development of new cancers drugs has been difficult and time consuming. However, the difficulty of such development is primarily a result of obtaining FDA approval in which not only substantial activity, but safety must also be demonstrated. For the purpose of enablement and patentability, there is no need that Applicants demonstrate that the compounds set forth in the claimed method are as active or more active than other compounds, or that such compounds are safe in administration. It is sufficient that the compounds are active to some extent in the claimed method. Once again, Applicants respectfully assert that activity of each of the compounds set forth in the claimed method is demonstrated to one skilled in the art in the specification.

In view of the above amendments and remarks, the Applicants respectfully requests that the Examiner, indicate the allowability of the Claims, and arrange for an official Notice of Allowance to be issued in due course.

Respectfully submitted,

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